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Hypofractionated external-beam radiation therapy (HEBRT) versus conventional external-beam radiation (CEBRT) in patients with localized prostate cancer: a systematic review and meta-analysis

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Background: The purpose of this work was to conduct a systematic review and meta-analysis of all randomized controlled trials comparing the efficacy and side effect profile of hypofractionated versus conventional external-beam radiation therapy for prostate cancer.

Methods: Several databases were searched, including Medline, EmBase, LiLACS, and Central. The endpoints were freedom from biochemical failure and side effects. We performed a meta-analysis of the published data. The results are expressed as the hazard ratio (HR) or risk ratio (RR), with the corresponding 95% confidence interval (CI).

Results: The final analysis included nine trials comprising 2702 patients. Freedom from biochemical failure was reported in only three studies and was similar in patients who received hypofractionated or conventional radiotherapy (fixed effect, HR 1.03, 95% CI 0.88–1.20; $P = 0.75$), with heterogeneity [$\chi^2 = 15.32$, df = 2 ($P = 0.0005$); $I^2 = 87\%$]. The incidence of acute adverse gastrointestinal events was higher in the hypofractionated group (fixed effect, RR 2.02, 95% CI 1.45–2.81; $P < 0.0001$). We also found moderate heterogeneity on this analysis [$\chi^2 = 7.47$, df = 5 ($P = 0.19$); $I^2 = 33\%$]. Acute genitourinary toxicity was similar among the groups (fixed effect, RR 1.19, 95% CI 0.95–1.49; $P = 0.13$), with moderate heterogeneity [$\chi^2 = 5.83$, df = 4 ($P = 0.21$); $I^2 = 31\%$]. The incidence of all late adverse events was the same in both groups (fixed effect, gastrointestinal toxicity, RR 1.17, 95% CI 0.79–1.72, $P = 0.44$; and acute genitourinary toxicity, RR 1.16, 95% CI 0.80–1.68, $P = 0.44$).

Conclusion: Hypofractionated radiotherapy in localized prostate cancer was not superior to conventional radiotherapy and showed higher acute gastrointestinal toxicity in this meta-analysis. Because the number of published studies is still small, future assessments should be conducted to clarify better the true role of hypofractionated radiotherapy in patients with prostate cancer.

Keywords: hypofractionated, radiotherapy, prostate cancer, systematic review, acute radiation effects

Introduction

Prostate cancer is the most common cancer in older men in the UK, the US, and western Europe.[1] Despite its high incidence, it will frequently respond to treatment when widespread, and may be cured when localized.[2] Radical prostatectomy and radiation therapy appear to yield similar survival rates with as many as 10 years of follow-up.[2]

The optimal external-beam radiation therapy (EBRT) schedule for the curative treatment of localized prostate carcinoma is still uncertain.[3–6] The National Comprehensive

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Cancer Network recommends that a three-dimensional technique or intensity-modulated radiation therapy (IMRT) should be used to treat prostate cancer. Doses of 75.6–79.2 Gy in conventional fractions to the prostate are appropriate for patients with low-risk cancers. For patients with intermediate-risk or high-risk disease, doses up to 81.0 Gy provide improved disease control as assessed by prostate-specific antigen (PSA).[7] Dose escalation and neoadjuvant androgen deprivation improve disease control, but the former increases side effects affecting the bowel.[8]

In ideal circumstances, the fractionation schedule of radiotherapy should match the fractionation sensitivity of the tumor relative to nearby normal tissues. A number of recent publications have suggested that the alpha-beta (α/β) ratio for the prostate is low, in the range of 1–3 Gy. If the α/β ratio is truly low, then hypofractionated schedules using fewer and larger fractions should improve the therapeutic results.[9] Hypofractionating external beam radiotherapy (HEBRT) with fractions $\geq$ 2.5 Gy per day can theoretically maintain high bioequivalent tumor doses without increasing acute and late toxicities, while decreasing treatment visits (which is convenient for patients), increasing treatment capacity, and reducing cost.[10]

Nonrandomized studies from the UK, Australia, Canada, the US, and Uruguay have reported that use of shorter radiation fractionation schedules[11–16] seemed to be comparable with conventional schedules. Although techniques using hypofractionating schemes have been in use for some time in the treatment of prostate cancer, there is limited experience with such schemes reaching doses $\geq$ 78 Gy.[17] Our objective was to analyze all published randomized controlled trials that compared the efficacy and side effect profile of hypofractionated versus conventional radiotherapy for prostate cancer.

Materials and methods

Study selection criteria

We included randomized controlled trials with a parallel design that compared the use of hypofractionated (ie, dose per fraction higher than 2.2 Gy) versus conventional radiotherapy (with doses per session ranging between 1.8 and 2.2 Gy). The studies selected included patients with localized prostate cancer without metastases.

Search strategy

A wide search of the main computerized databases was conducted, including EmBase, LiLACS, Medline, Science Citation Index, the National Cancer Institute Clinical Trials service, and the Clinical Trials Register of Trials Central. In addition, abstracts published in the proceedings of the American Society of Clinical Oncology, American Society of Radiation Oncology (ASTRO), European Society of Medical Oncology, Society of Urologic Oncology, and European Society for Radiotherapy and Oncology were also searched.

For Medline, we used the search strategy methodology for randomized controlled trials[18] recommended by the Cochrane Collaboration.[19] For EmBase, we used adaptations of this same strategy,[18] and for LiLACS, we used the search strategy methodology reported by Castro et al.[20] We performed an additional search in the Science Citation Index database looking for articles that were cited in the included studies. We added specific terms pertinent to this review to the overall search strategy methodology for each database.

The overall search strategy was: #1 prostatic neoplasms (MeSH Terms), #2 radiotherapy (MeSH Terms), #3 hypofractionated (All Fields), and #4 randomized controlled trial (ptyp). Searches in electronic databases combined the terms #1 AND #2 AND #3 AND #4.

Critical evaluation of selected studies

All the references retrieved by the search strategies had their title and abstract evaluated by two of the researchers. Every reference with the least indication of fulfilling the inclusion criteria was listed as preselected. We retrieved the complete articles of all preselected references. These were analyzed by two different researchers and included or excluded according to the criteria previously described. The excluded trials and the reason of their exclusion are listed in this paper. Data were extracted from all the included trials.

Details regarding the main methodology characteristics empirically linked to bias[21] were extracted, with the methodological validity of each selected trial assessed by two reviewers (TEAB and OC).

Data extraction

Two independent reviewers extracted the data. The name of the first author and year of publication were used to identify the study. All data were extracted directly from the text or calculated from the available information when necessary. The data from all trials were based on the intention-to-treat principle, so they compared all patients allocated to one treatment with all those allocated to another.

The primary endpoint was freedom from biochemical failure (FFBF). FFBF was defined as the interval from the first day of radiotherapy to the date of biochemical relapse, defined according to the most recent Phoenix definition,[22]

ie, the nadir PSA level plus 2 μg/mL, or the ASTRO definition.[23]

Other clinical outcomes were also evaluated, ie, biochemical failure rate, death from tumor rate, and number of patients with adverse events (gastrointestinal and genitourinary, grade ≥ 2). Toxicity was evaluated using the Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer system[24] summarized as: grade 1, minimal side effects not requiring medication; grade 2, symptoms requiring medication; grade 3, requiring minor surgical intervention (transurethral resection, laser coagulation, or blood transfusion); and grade 4, hospitalization and major intervention. Late toxicity was defined as rectal or urinary symptoms occurring or persisting for ≥6 months after the end of radiotherapy.

Analysis and presentation of results

The data were analyzed using the Review Manager 5.0.24 statistical package (Cochrane Collaboration Software).[25] Dichotomous clinical outcomes are reported as the risk ratio (RR) and survival data as the hazard ratio (HR).[26] The corresponding 95% confidence interval (CI) was calculated, considering P values less than 5% ($P < 0.05$). A statistic for measuring heterogeneity was calculated using the I_2 method, whereby 25% was considered to be low-level heterogeneity, 25%–50% moderate-level heterogeneity, and >50% high-level heterogeneity.[27,28]

To estimate the absolute gains in FFBF, we calculated the meta-analytic survival curves as suggested by Parmar et al.[26] A pooled estimate of the HR was computed by a fixed-effect model according to the inverse variance method.[29] Thus, for effectiveness or side effects, an HR or RR > 1 favors the standard arm (conventional), whereas an HR or RR < 1 favors hypofractionated treatment.

If statistical heterogeneity was found in the meta-analysis, we performed an additional analysis using the random-effects model described by DerSimonian and Laird,[30] which provides a more conservative analysis.

To assess the possibility of publication bias, we used the funnel plot test described by Egger et al.[31] When the pooled results were significant, the number of patients needed to treat to cause or to prevent one event was calculated by pooling absolute risk differences in the trials included in this meta-analysis.[32–34] For all analysis, a forest plot was generated to display the results.

Results

Figure 1 shows the flow of identification and inclusion of trials, as recommended by the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) statement.[35] Overall, 171 references were identified and screened. Twenty studies were selected and retrieved for full-text analysis. Of these, 11 were excluded for various reasons, as described in the additional material presented in Table 1. Details on treatment modality, follow-up, risk group definitions, tumor node metastasis or biochemical failure definitions, and gastrointestinal and genitourinary toxicity in the 11 trials included in the analysis are summarized in Tables 2–5. The total dose of radiation therapy varied among the studies (conventional 64–80 Gy and hypofractionated 52.5–72 Gy) as well as tumor node metastasis and risk (Table 2).

The clinical target volume, in most studies, involved the prostate and seminal vesicles (total or partial). The clinical target volume was the prostate gland alone with a 1.5 cm margin only in two studies.[4,36–38] The most frequent planning target volume was a clinical target volume with a margin of 0.8–1.0 cm (Table 3). Although nine randomized trials on the topic have been included in this analysis, only three studies[4,17,36–39] reported data on FFBF (Table 4). Overall, the FFBF was similar in patients who received hypofractionated or conventional radiotherapy (fixed effect, HR 1.03, 95% CI 0.88–1.20; $P = 0.75$), with high heterogeneity [$\chi^2 = 15.32$, df = 2 ($P = 0.0005$); $I^2 = 87\%$, Figure 2]. Two of the studies used the Phoenix definition for FFBF[17,36–39] and one used the ASTRO definition.[4]

The number of patients who had biochemical failure was also similar between the groups (fixed effect, RR 0.99, 95% CI 0.87–1.12; $P = 0.85$) with moderate heterogeneity [$\chi^2 = 7.94$, df = 5 ($P = 0.16$); $I^2 = 37\%$, Figure 3]. Death from tumor also did not differ between the groups (fixed effect, RR 0.34, 95% CI 0.09–1.23; $P = 0.10$). PSA nadirs ≤ 0.5 ng/mL were reported in two studies[17,39–41] and were similar.

Gastrointestinal and genitourinary acute adverse event data were obtained from six studies[4,8,17,39–42,44–47] (Table 5). The incidence of acute adverse gastrointestinal events (grade ≥ 2) was higher in the hypofractionated group (fixed effect, RR 2.02, 95% CI 1.45–2.81; $P < 0.0001$; number needed to harm = 25). We also found moderate heterogeneity on this analysis [$\chi^2 = 7.47$, df = 5 ($P = 0.19$); $I^2 = 33\%$, Figure 4]. Two studies[4,36–38] used the two-dimensional technique, and the toxicity rates did not differ between the groups. As planned, we performed a random-effects model analysis, and the results remained favorable for conventional radiotherapy (random effects, RR 1.87, 95% CI 1.20–2.93; $P = 0.006$).

In most studies, acute toxicity was evaluated using the Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer system[24] and late side

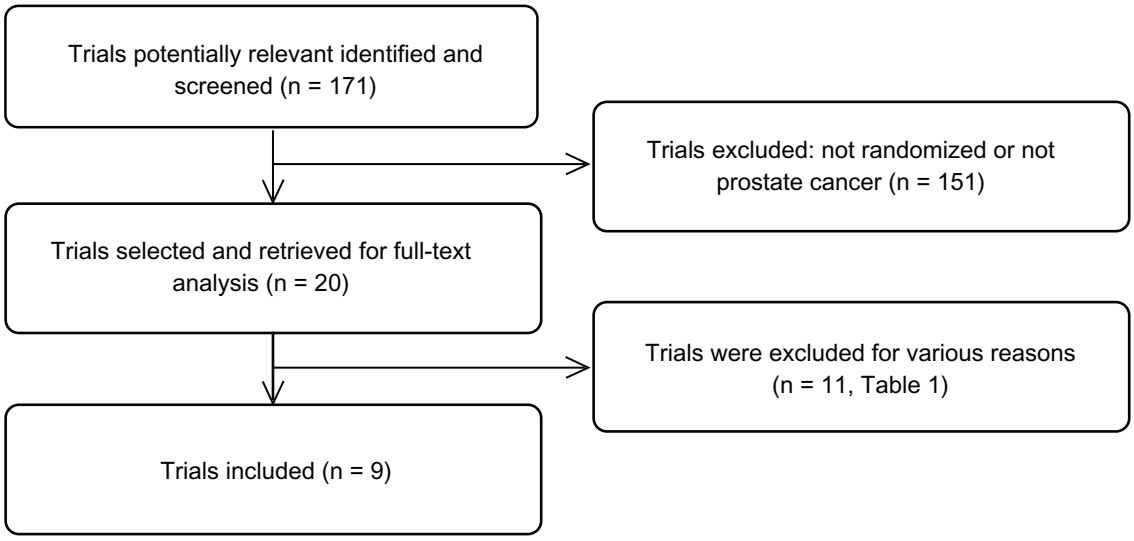

Figure 1 Trial selection flow.

effects were evaluated using the LENT/SOMA (Late Effects in Normal Tissues Subjective, Objective, Management and Analytic) scale.[49,50] Acute genitourinary toxicity was similar among the groups (fixed effect, RR 1.19, 95% CI 0.95–1.49; $P = 0.13$), with moderate heterogeneity [$\chi^2 = 5.83$, df = 4 ($P = 0.21$); $I^2 = 31\%$, Figure 4]. Gastrointestinal or genitourinary late adverse event data were also obtained from six studies[4,8,17,39,43,45–48] (Table 5). The incidence of all late adverse events was the same for both groups (fixed effect, gastrointestinal, RR 1.17, 95% CI 0.79–1.72; $P = 0.44$ and genitourinary, RR 1.16, 95% CI 0.80–1.68; $P = 0.44$). We found no heterogeneity on this analysis [gastrointestinal toxicity, $\chi^2 = 3.74$, df = 5 ($P = 0.59$), $I^2 = 0\%$; and genitourinary toxicity, $\chi^2 = 2.73$, df = 4 ($P = 0.60$), $I^2 = 0\%$, Figure 5].

Subgroup analysis

Three studies[4,37,38,40–42,51] did not use hormonal therapy concomitant with radiotherapy. Two of them[4,40–42] reported toxicity data. Acute gastrointestinal toxicity was similar between the groups (fixed effect, RR 1.51, 95% CI 0.78–2.92; $P = 0.22$). Hormonal therapy was permitted in six of the trials,[8,17,39,43–48] and acute gastrointestinal toxicity was greater in the HEBRT arm (fixed effect, RR 2.23, 95% CI 1.52–3.27; $P < 0.0001$), with moderate heterogeneity [$\chi^2 = 6.70$, df = 3 ($P = 0.08$); $I^2 = 55\%$]. When the analysis was performed using the random-effects model, the results remained favorable for CEBRT (random effect, RR 2.04, 95% CI 1.05–3.98; $P = 0.04$).

When we analyzed the subgroup of patients who received only conventional higher doses of radiotherapy (≥78 Gy) versus hypofractionated radiotherapy, only one study[17,39] with 168 patients reported FFBF and biochemical failure data, making it impossible to perform this meta-analysis. In this particular study, the FFBF was favorable for HEBRT (HR 0.354, 95% CI 0.22–0.58; $P = 0.004$). In a subgroup of patients who received doses from 74 to 77.9 Gy in conventional fractions, the FFBF results were not reported.[8,45–48] The number of patients with biochemical failure was also similar between the groups (fixed effect, RR 0.90, 95% CI 0.54–1.47; $P = 0.66$), with no heterogeneity [$\chi^2 = 0.25$, df = 2 ($P = 0.88$); $I^2 = 0\%$].

Regarding the acute gastrointestinal toxicity in the three studies[17,39,43,44] that used conventional higher doses of radiotherapy (≥78 Gy), the hypofractionated group also showed a higher level of toxicity (fixed effect, RR 2.48, 95% CI 1.61–3.81; $P < 0.0001$). In this analysis, there was significant heterogeneity [$\chi^2 = 4.51$, df = 1 ($P = 0.03$); $I^2 = 78\%$, Figure 6]. However, when the analysis was performed using the random-effects model, no significant

Table 1 Characteristics of excluded studies

Study	Reason for exclusion
Martin et al[60]	Not a randomized trial
Messai et al[61]	Not a randomized trial
McDonald et al[62]	Not a randomized trial
Barnett et al[63]	Different comparison
Syndikus et al[64]	Different comparison
Viani et al[53]	Meta-analysis of randomized controlled trials
Whelan et al[65]	Not prostate cancer
Sundstrom et al[66]	Not prostate cancer
Siegel et al[67]	Not prostate cancer
Shahid et al[68]	Not prostate cancer
Read and Pointon[13]	Not a randomized trial

Table 2 Characteristics of studies included for localized prostate cancer

Study	n	TNM or risk group	RT	Design	Schedule	ADT	Primary endpoint
Yeoh et al[36–38]	108 109	T1–T2N0M0 PSA < 80	Most 2D method	Hypofractionated versus conventional	55 Gy (20 fractions of 2, 7 Gy, 4 wks) 64 Gy (32 fractions within 6.5 wks)	No	Late radiation morbidity
Arcangeli et al[17,39]	83 85	≥T2c, Gleason ≥ 7 PSA ≥ 20	3D conformal method	Hypofractionated versus conventional	62 Gy (20 fractions of 3.1 Gy, 5 wks) 80 Gy (40 fractions of 2 Gy, 8 wks)	Yes	Rates of late complications
Dearnaley et al[8]	153 151 153	T1–T3N0M0 and PSA < 30 ng/mL	IMRT	Hypofractionated vs hypofractionated versus conventional	60 Gy (20 fractions of 3 Gy) 57 Gy (19 fractions of 3 Gy) 74 Gy (37 fractions of 2 Gy)	Yes	Toxicity ≥ grade 2
Norkus et al[40–42]	47 44	T1–3N0M0 and PSA ≤ 10, Gleason < 7	3D conformal method	Hypofractionated versus conventional	57 Gy (13 fractions of 3 Gy plus 4 fractions of 4.5 Gy) 74 Gy (37 fractions of 2 Gy)	No	Overall survival, FFBF, biochemical response, toxicity
Marzi et al[43]	57 57	T2c–T4, PSA > 10 ng/mL, Gleason 7–10	3D conformal method	Hypofractionated versus conventional	62 Gy (20 fractions of 3.1 Gy, 5 wks) 80 Gy (40 fractions over 8 wks)	Yes	Toxicity ≥ grade 2
Strigari et al[44]	80 52 80	localized prostate cancer	3D conformal method	Hypofractionated versus hypofractionated (IMRT) versus conventional	62 Gy (20 fractions of 3.1 Gy, 4 d/wk) 56 Gy (16 fractions of 3.5 Gy, 4/wk) 80 Gy (40 fractions within 8 wks)	Yes	Toxicity ≥ grade 2
Lukka et al[4]	466 470	T1–2N0M0 and PSA < 40	2D method	Hypofractionated versus conventional	52.5 Gy (20 fractions of 2.6 Gy, 28 days) 66 Gy (33 fractions over 45 days)	No	Biochemical or clinical failure
*Pollack et al[45–47]	151 152	T1–3N0M0 intermediate to high-risk	IMRT	Hypofractionated versus conventional	70.2 Gy (26 fractions of 2.7 Gy) 76 Gy (38 fractions of 2.0 Gy)	Yes	FFBF
Kuban et al[48]	102 102	Low and intermediate-risk	IMRT	Hypofractionated versus conventional	72 Gy (30 fractions of 2.4 Gy) 75.6 Gy (42 fractions of 1.8 Gy)	Yes	Biochemical or clinical failure and toxicity

Abbreviations: RT, radiotherapy; wks, weeks; 2D, two-dimensional; 3D, three-dimensional; ADT, androgen deprivation therapy; IMRT, intensity-modulated radiation therapy; FFBF, freedom from biochemical failure; TNM, tumor node metastasis; PSA, prostate-specific androgen.
Note: *Late toxicity data were extracted with the publication Turaka A, et al. 2010.

difference was detected (random effect, RR 2.58, 95% CI 0.94–7.05; $P = 0.06$).

In the subgroup of patients who only used IMRT, the FFBF results were not reported for either CEBRT or HEBRT.[8,45–48] The number of patients with biochemical failure was also similar between the groups (fixed effect, RR 0.93, 95% CI 0.55–1.56; $P = 0.78$) with no heterogeneity [$\chi^2 = 0.06$, df = 1 ($P = 0.80$); $I^2 = 0\%$]. Acute gastrointestinal and genitourinary toxicity was also similar (fixed effect, RR 1.46, 95% CI 0.62–3.43, $P = 0.38$; RR 0.92, 95% CI 0.64–1.31, $P = 0.64$, respectively, Figure 7), as well as the incidence of late adverse events (fixed effect for gastrointestinal toxicity, RR 1.30, 95% CI 0.73–2.32, $P = 0.37$; fixed effect for genitourinary toxicity, RR 1.16 95% CI 0.75–1.79, $P = 0.51$), with moderate and low heterogeneity, respectively (Figure 8). In these three studies,[8,45–48] the use of hormonal therapy was permitted.

In the subgroup of patients who received only the three-dimensional technique for both CEBRT and HEBRT,[17,39–44] only Arcangeli et al[17,39] reported FFBF data. In this particular

Table 3 Definition of target volumes used in the trials

Study	CTV	PTV
Yeoh et al[36–38]	Prostate gland alone with a 1.5 cm margin	Prostate + base of seminal vesicles
Arcangeli et al[17,39]	Prostate + seminal vesicles	CTV with a margin of 1 cm in each direction, and of 0.6 cm posteriorly
Dearnaley et al[8]	Low risk: prostate + base of seminal vesicles + 0.5 cm Moderate risk: prostate + seminal vesicles + 0.5 cm	CTV with a margin of 1 cm in each direction and of 0.5 cm posteriorly
Norkus et al[40–42]	Prostate + base of seminal vesicles	CTV plus a uniform expansion of 0.8–1 cm in all directions
Marzi et al[43]	Prostate + seminal vesicles	CTV with a margin of 1 cm in each direction and of 0.6 cm posteriorly
Strigari et al[44]	Prostate + seminal vesicles (except stage T1–T2 = prostate only)	CTV plus a uniform expansion of 0.8 cm in all directions
Lukka et al[4]	Prostate gland alone with a 1.5 cm margin	Margin of 1.5 cm in each direction and of 1.0 cm posteriorly
Pollack et al[45–47]	Intermediate risk: prostate + proximal seminal vesicles (approximately 9 mm) High-risk: prostate + 50% of the seminal vesicles and pelvic lymph nodes	Conventional: CTV with a margin of 0.8 cm in each direction and of 0.5 cm posteriorly Hypofractionated: CTV with a margin of 0.7 cm in each direction and of 0.3 cm posteriorly
Kuban et al[48]	NR	NR

Abbreviations: CTV, clinical target volume; PTV, planning target volume; NR, not reported.

Table 4 Efficacy analysis in the trials included in the meta-analysis

Study	Design	n	BF	FFBF	nPSA ≤0.5 ng/mL	Death from tumor	Median follow-up
Yeoh et al[36–38]	Hypofractionated Conventional	108 109	36 (33.3%) 49 (44.9%) $P < 0.05$	57 (53%) 37 (34%) $P < 0.05$; HR 0.65 95% CI (0.42–0.99)	NR	2 (1,85%) 4 (3.66%)	7.5 years
Arcangeli et al[17,39]	Hypofractionated Conventional	83 85	8 (10%) 16 (19%) $P = 0.14$	68 (82%) 51 (60%) $P = 0.004$ HR 0.354 95% CI (0.22–0.58)	83 (100%) 80 (94%) P = NS	0 (0%) 1 (1%) $P = 0.99$	2.9 years
Dearnaley et al[8]	Hypofractionated (60 Gy) Hypofractionated (57 Gy) Conventional	153 151 153	NR	NR	NR	NR	4.2 years
*Norkus et al[40–42]	Hypofractionated Conventional	47 44	2 (4.25%) 3 (6.81%)	NR	8 (18.2%) 10 (25%) $P = 0.62$	0 (0%) 0 (0%)	1 year
Marzi et al[43]	Hypofractionated Conventional	57 57	NR	NR	NR	NR	2.5 years
Strigari et al[44]	Hypofractionated (62 Gy) Hypofractionated (56 Gy) IMRT Conventional	80 52 80	NR	NR	NR	NR	<2 months
*Lukka et al[4]	Hypofractionated Conventional	466 470	217 (47%) 199 (42%)	**HR 1.18 (95% CI, 0.99–1.41) in favor of conventional	NR	0 (0%) 3 (1.0%)	5.7 years
Pollack et al[45–47]	Hypofractionated Conventional	151 152	20 (13.9%) 21 (14.4%)	NR	NR	NR	5 years
Kuban et al[48]	Hypofractionated Conventional	102 102	4 (3.92%) 5 (4.9%)	NR	NR	0 (0%) 0 (0%)	4.6 years

Notes: *FFBF was defined as American Society for Therapeutic Radiology and Oncology Consensus,[23] ie, three consecutive increases in PSA is a reasonable definition of biochemical failure after radiation therapy. **Freedom from biochemical or clinical failure.
Abbreviations: nPSA, nadir prostate specific antigen; FFBF, freedom from biochemical failure; BF, biochemical failure; NR, not reported; NS, not significant.

Table 5 Gastrointestinal and genitourinary toxicity in the trials included in the meta-analysis

Study	Design	n	Toxicity gastrointestinal (grade ≥ 2)		Toxicity genitourinary (grade ≥ 2)	
			Acute	Late	Acute	Late
Yeoh et al[36–38]	Hypofractionated	108	NR	NR	NR	NR
	Conventional	109	*P* = NS	*P* = NS	*P* = NS	*P* = NS
Arcangeli et al[17,39]	Hypofractionated	83	29 (35%)	12 (14%)	39 (47%)	7 (8%)
	Conventional	85	18 (21%)	10 (12%)	34 (40%)	5 (6%)
			P = 0.07	*P* = 0.55	*P* = 0.45	*P* = 0.092
Dearnaley et al[8]	Hypofractionated (60 Gy)	153	3 (2.3%)	5 (3.6%)	10 (7.6%)	3 (2.2%)
	Hypofractionated (57 Gy)	151	1 (0.8%)	2 (1.4%)	9 (7.0%)	0 (0%)
	Conventional (74 Gy)	153	3 (2.3%)	6 (4.3%)	9 (7.0%)	3 (2.2%)
Norkus et al[40–42]	Hypofractionated	47	**2 (18.18%)	NR	**2 (18.18%)	NR
	Conventional	44	**2 (18.18%)		**3 (27.27%)	
Marzi et al[43]	Hypofractionated	57	NR	7 (12.3%)	NR	NR
	Conventional	57		8 (14.0%)		
				P = 0.688		
Strigari et al[44]	Hypofractionated (62 Gy)	80	20 (25%)	NR	NR	NR
	Hypofractionated (56 Gy)	52	22 (42.5%)			
	Conventional	80	6 (8.0%)			
			P < 0.0001			
Lukka et al[4]	Hypofractionated	466	*19 (4.1%)	6 (1.3%)	40 (8.6%)	9 (1.9%)
	Conventional	470	12 (2.6%)	6 (1.3%)	23 (4.9%)	9 (1.9%)
Pollack et al[45,47]	Hypofractionated	151	**9 (18%)	9 (5.9%)	**24 (48%)	21 (13.8%)
	Conventional	152	**4 (8%)	6 (4.1%)	**28 (56%)	13 (8.9%)
			P = NS	*P* = 0.754	*P* = NS	*P* = 0.041
Kuban et al[48]	Hypofractionated	102	NR	11 (10%)	NR	15 (19%)
	Conventional	102		5 (4.9%)		16 (19%)
				P = NS		*P* = NS

Note: *Toxicity grade ≥ III; **toxicities extracted from the first publication.
Abbreviations: NR, not reported; NS, not significant.

study, FFBF was favorable for HEBRT (HR 0.354, 95% CI 0.22–0.58; *P* = 0.004). The number of patients with biochemical failure was also similar between the groups (fixed effect, RR 0.53, 95% CI 0.26–1.09; *P* = 0.08), with no heterogeneity [$\chi^2 = 0.04$, df = 1 (*P* = 0.84); $I^2 = 0\%$].

Acute gastrointestinal toxicity was higher in the hypofractionated group (fixed effect, RR 2.37, 95% CI 1.56–3.60; *P* < 0.0001; number needed to harm = 7), with significant heterogeneity [$\chi^2 = 5.22$, df = 2 (*P* = 0.07); $I^2 = 62\%$]. However, when the analysis was performed using the random-effects model, no significant difference was detected (random effect, RR 2.20, 95% CI 0.96–5.04; *P* = 0.06). Acute genitourinary toxicity was similar (RR 1.13, 95% CI 0.81–1.59; *P* = 0.47), as was the incidence of late adverse events (fixed effect for gastrointestinal toxicity, RR 1.07, 95% CI 0.59–1.95, *P* = 0.82; fixed effect for genitourinary toxicity, RR 1.43, 95% CI 0.47–4.34, *P* = 0.52). Three[17,39,43,44] of the four studies that used the three-dimensional technique permitted use of concomitant hormonal therapy.

According to the funnel plot analysis,[31] the possibility of publication bias was low for all of the outcomes. When the funnel plot shows asymmetry, there is the possibility

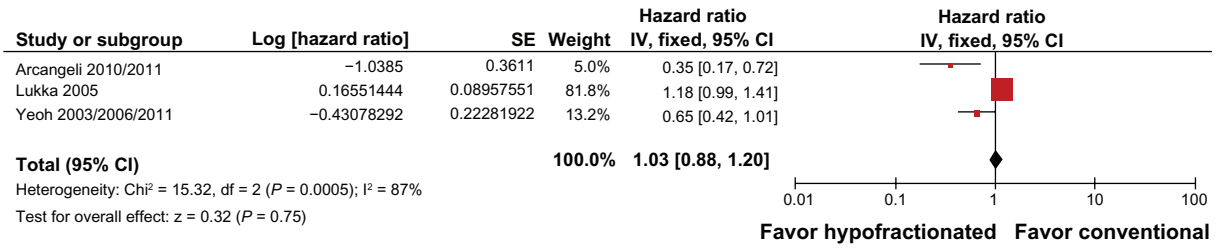

Figure 2 Comparative effect in freedom from biochemical failure of hypofractionated or conventional radiotherapy.

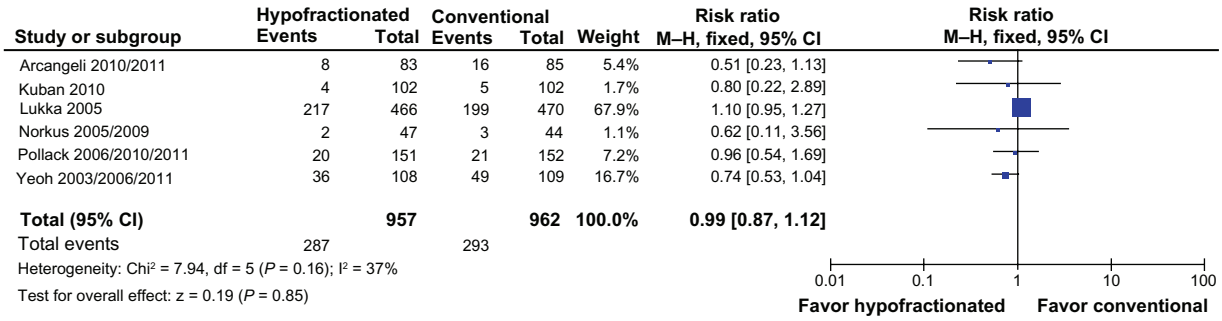

Figure 3 Comparative effect in biochemical failure of hypofractionated or conventional radiotherapy.

of publication bias. This method has its limitations, but nonetheless is used widely to assess publication bias.

Discussion

Higher doses of radiotherapy have proven to be more effective for controlling localized prostate cancer. A randomized study with a total of 301 patients with stage T1b to T3 prostate cancer evaluated treatment with 70 Gy doses versus 78 Gy.[52] FFBF was superior for the 78 Gy arm (78%), as compared with the 70 Gy arm (59% $P = 0.004$), and an even greater benefit was seen in patients with initial PSA $>$ 10 ng/mL (78% versus 39%, $P = 0.001$).[52]

A meta-analysis published later[53] confirmed these data, showing that higher doses of radiotherapy were superior in preventing biochemical failure in patients with low-risk, intermediate-risk, and high-risk prostate cancer, suggesting that this should be offered as the standard of treatment for all patients, regardless of their risk status.

Overall survival is certainly the outcome of greatest importance for any cancer therapy because it incorporates the effect of mortality secondary to cancer, the interventions used, and all other causes. Given the relatively indolent natural history of prostate cancer, it is anticipated that lengthy follow-up is necessary to assess differences in overall survival.[54]

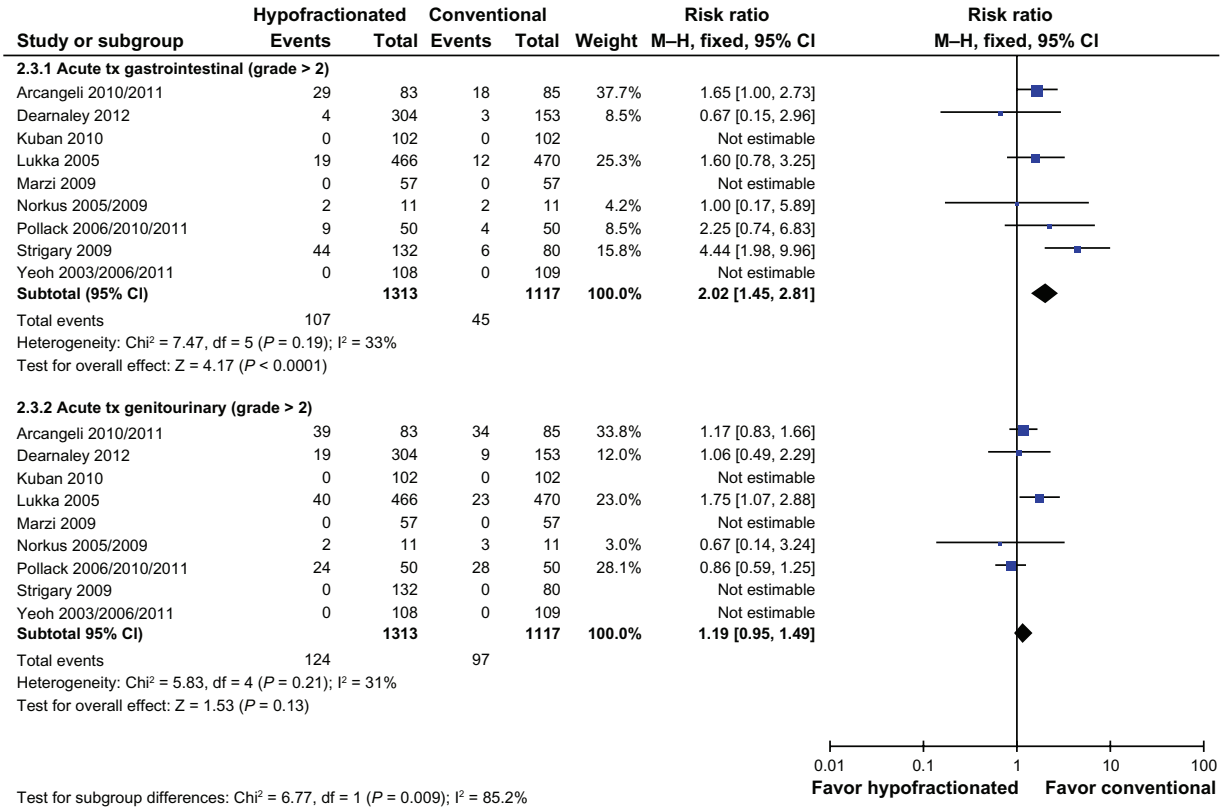

Figure 4 Incidence of acute adverse events (grade $>$ 2) of hypofractionated or conventional radiotherapy.

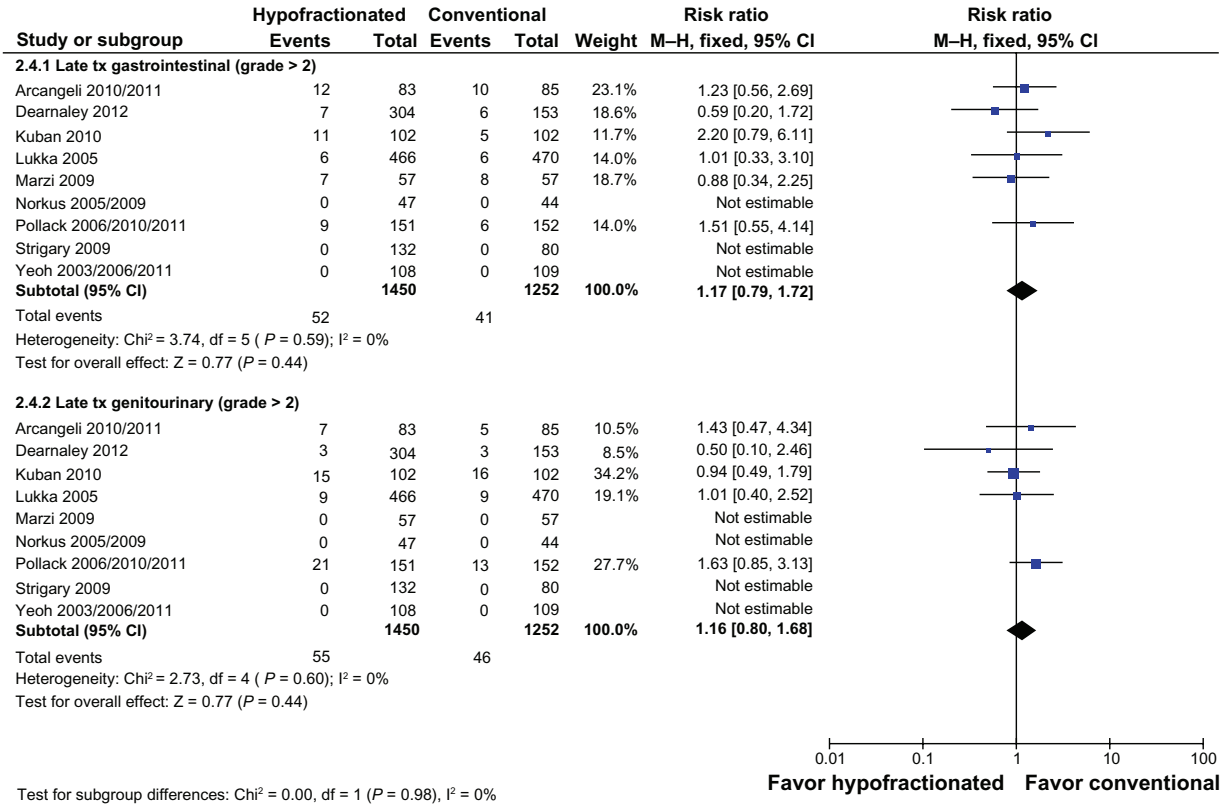

Figure 5 Incidence of late adverse events (grade > 2) of hypofractionated or conventional radiotherapy.

In the present meta-analysis, FFBF was similar between the HEBRT and conventional arms, despite only three studies[4,17,36–39] reporting FFBF data. However, as noted, only one study[17,39] used the conventional dose of CEBRT ≥ 78 Gy. The other two[4,36–38] used lower and similar doses, both for the HEBRT and for the conventional arm (Yeoh et al used hypofractionated 55 Gy and conventional 64 Gy; Lukka et al used hypofractionated 52.5 Gy and conventional 66 Gy). In the study that used the higher conventional dose,[17,39] the FFBF was favorable for HEBRT ($P = 0.004$). Because the median follow-up of this study was small (2.9 years), conclusions concerning optimal disease control are limited.

The biochemical failure rate was generally similar between the radiotherapy regimens. However, when the studies by Lukka et al[4] and Norkus et al,[40–42] which used the ASTROS criteria for biochemical failure, were withdrawn, the biochemical failure rate was also favorable for HEBRT.

Although the ASTRO definition is the most widely accepted one for PSA failure, it is associated with limitations.[55,56] The nadir PSA level ≥ 2 or 3 µg/L definition of biochemical failure was proposed to replace the ASTRO[23] parameters at the Phoenix Consensus Conference,[22] because it has been reported to be more sensitive and specific for the determination of ultimate clinical failure. Duration of hormone therapy varied between 2 and 6 months neoadjuvantly/concomitantly, and only one study used it for 2 years in high-risk patients.[45,46]

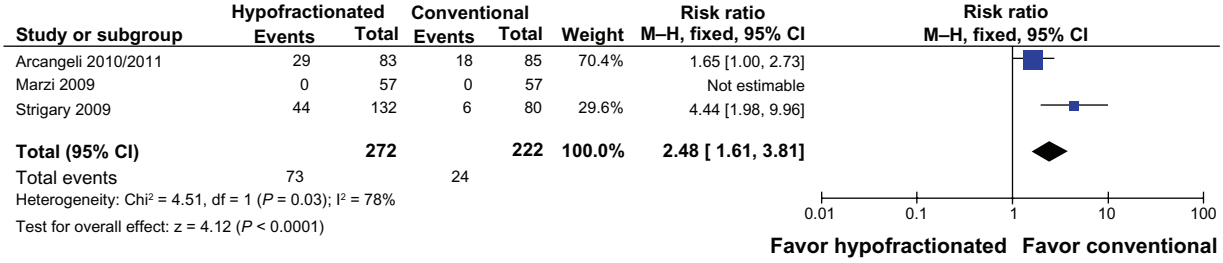

Figure 6 Incidence of acute adverse events (grade > 2) of hypofractionated or conventional radiotherapy (>78 Gy).

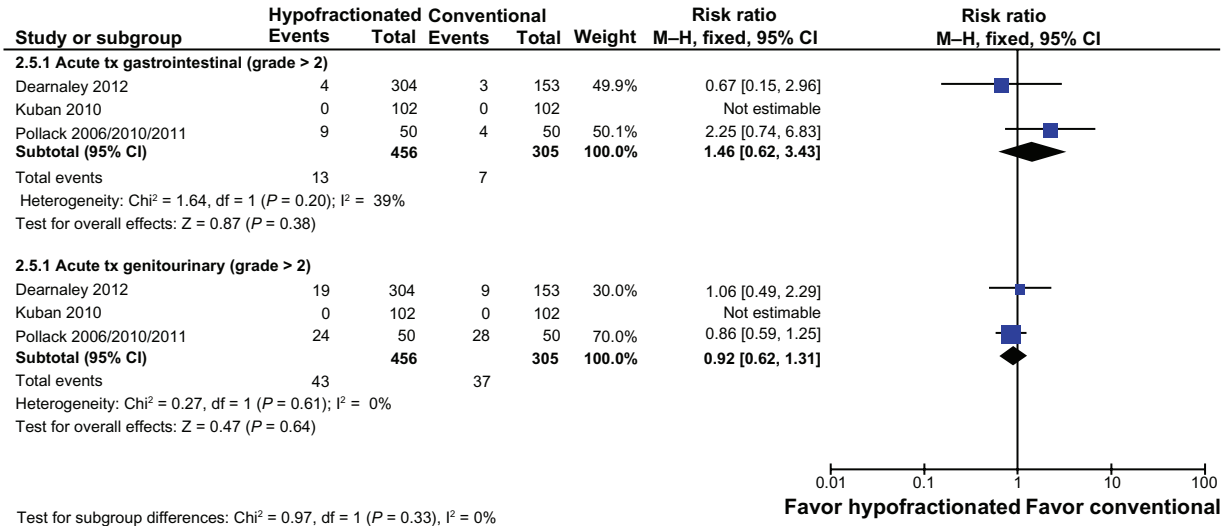

Figure 7 Incidence of acute adverse events (grade > 2) of hypofrationated or conventional radiotherapy (only intensity-modulated radiotherapy).

Overall, there were more acute gastrointestinal side effects in the group that used HEBRT. The side effects were even more accentuated when HEBRT was compared with higher doses of CEBRT (≥78 Gy) and when the three-dimensional technique was used with concomitant hormonal therapy. However, no significant difference was detected when the analysis was performed using the random-effects model. Because random-effects models provide a more conservative estimate of the average treatment effect when trials are statistically heterogeneous,[30] we cannot really say whether HEBRT is more toxic when compared with higher doses of CEBRT. A definitive answer will come as more studies are published.

When IMRT was used, the gastrointestinal toxicity (acute and late) did not differ between the groups (HEBRT versus CEBRT), even when use of concomitant hormonal therapy was permitted, but again, the studies that used this technique used lower doses of conventional radiotherapy (74–76 Gy). With this radiotherapy technique, only Pollack et al[46] and Kuban et al[48] reported efficacy (biochemical failure rate) data that were similar over 4–5 years.

An abbreviated course of radiotherapy is more convenient to the patient and possibly less expensive than standard treatment. Some studies are in progress evaluating the use of extreme HEBRT with fractions ≥ 6.1 Gy/day.[57,58]

The lack of evidence of a long-term therapeutic advantage for hypofractionated compared with conventional radiotherapy dose schedules for prostate cancer is a major obstacle to the adoption of hypofractionated dose schedules

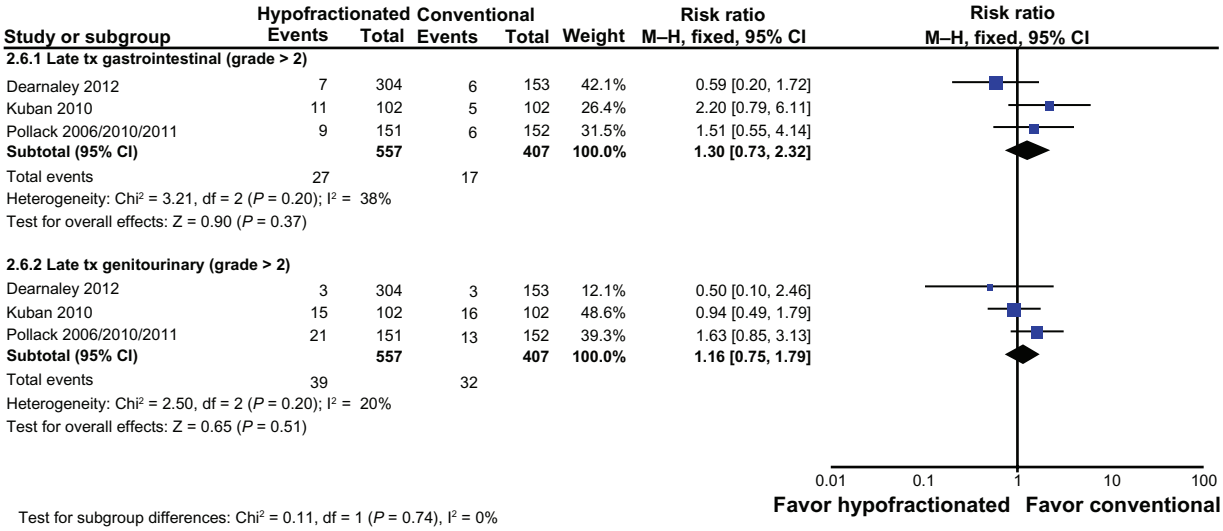

Figure 8 Incidence of late adverse events (grade > 2) of hypofractionated or conventional radiotherapy (only intensity-modulated radiotherapy).

in clinical practice.[59] To our knowledge, this was the first meta-analysis on this topic.

Conclusion

Acute gastrointestinal toxicity was higher in the group of patients treated with HEBRT especially when compared with the use of higher doses of CEBRT. When the IMRT technique was used, this difference seemed to decrease. In general, HEBRT was safe with acceptable complication rates.

Overall, in terms of efficacy, the results of HEBRT in localized prostate cancer were not superior to conventional therapy in this meta-analysis. In the study that used the higher conventional dose (≥78 Gy), the FFBF was favorable to HEBRT but the number of patients and the median follow-up of this study was small, so conclusions concerning the best disease control are limited. Future assessments should be conducted to clarify better the real role of hypofractionated radiotherapy in patients with prostate cancer.

Disclosure

The authors report no conflicts of interest in this work.

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